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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,860	10/13/2000	Vinod Asundi	28110/36737	1298

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	10

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/687,860	ASUNDI ET AL.	
	Examin r	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondenc address --

Period f r R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 10 December 2002 (Paper No. 9) and 24 April 2002 (Paper No. 5) have been entered in full. Claims 43-58 are added, claims 46-58 are amended, and claims 1-42 are cancelled.

Claims 43-58 are under consideration in the instant application.

Election/Restrictions

Applicant's election without traverse of the species of biological sample (tissue/cell/blood/serum) and cancerous cell type (colon cancer cell) in Paper No. 9 (10 December 2002) is acknowledged. It is noted that the Examiner has rejoined the species of cancerous cell type type.

The Examiner acknowledges Applicant's request of rejoinder of Groups (b-d) upon the allowance of product claims.

Drawings

1. The corrected or substitute drawings were received on 24 April 2002 (Paper No. 5). These drawings are acceptable.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Applicant has not given a post office address anywhere in the application papers as required by 37 CFR 1.33(a), which was in effect at the time of filing of the oath or declaration. A statement over applicant's signature providing a complete post office address is required.

Specification

3. The disclosure is objected to because of the following informalities:

3a. An updated status of the parent nonprovisional application should be included in the first sentence of the specification. A statement reading "This is a continuation-in-part of U.S. Application Serial No. 09/620,312, filed July 19, 2000, U.S. Patent No. 6,569,662, which is a continuation-in-part of U.S. Applicant Serial No. 09/363,316, filed July 28, 1999, U.S. Patent No. 6,392,019" should be entered.

3b. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See for example, pg 105, line 29). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

3c. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD OF DETECTING A CANCEROUS CELL EXPRESSING AN EGF MOTIF PROTEIN".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 43-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Briefly, the claims are directed to a method of detecting a cancerous cell expressing the polypeptide of SEQ ID NO: 24 or a fragment thereof in a biological sample, comprising (a) contacting the sample with an antibody or fragment thereof that specifically binds to the polypeptide of SEQ ID NO: 24 or a fragment thereof for a time period sufficient to form a complex; (b) detecting the complex, so that if a complex is detected it indicates the presence of the cancerous cell; and (c) comparing said expression to a standard indicative of cancer. The claims also recite that the polypeptide fragment comprises the amino acids 22-553 of SEQ ID NO: 24 or amino acids 412-426 of SEQ ID NO: 24. The claims recite that the antibody is conjugated to a radioisotope, affinity label, enzymatic label, or fluorescent label. The claims recite that the biological is selected from the group consisting of tissue, cell, blood, serum, lymphatic fluid, urine, and cerebrospinal fluid. Additionally, the claims recite that the cancerous cell is selected from the group consisting of a brain cancer, prostate cancer, breast cancer, skin cancer, lymphoma, sarcoma, colon cancer, leukemia, ovarian cancer, and pancreatic cancer cell.

The specification teaches that differential expression of the EGFL6 mRNA transcript was detected in placenta, tonsil, prostate carcinoma, colon carcinoma, lung carcinomas, breast carcinoma, and to a lesser extent in normal breast (pg 109, lines 18-20). The specification also discloses that very strong signals were detected in prostate, breast and colon carcinoma and that

the EGFL6 transcript did not appear to be expressed in nomal prostate, normal colon, or normal lung (pg 109, lines 21-22). Although the specification teaches that the EGFL6 mRNA transcript is differentially expressed in cancerous tissues v. normal tissues, the specification does not disclose any specific resulting numbers or percentages, statistical differences, or the cancer grades for the cancerous tissue samples. Without this knowledge, which could not be gleaned from the instant specification, one of ordinary skill in the art at the time the invention was made would not have been able to use the information obtained from this assay in a useful manner.

The specification also does not teach an antibody or antibody fragment that specifically binds to the polypeptide of SEQ ID NO: 24. The specification does not teach any methods or working examples that detect all cancerous cells expressing the polypeptide of SEQ ID NO: 24 or all possible fragments of SEQ ID NO: 24 in all possible types of biological samples. The specification does not teach detection of EGFL6 *protein expression* in any cancers. Although the specification teaches that EGFL6 mRNA transcript is expressed in placenta, tonsil, prostate carcinoma, colon carcinoma, lung carcinoma, and breast carcinoma (pg 109), the state of the art is such that protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript (Haynes et al., Electrophoresis 19:1862-1872, 1998). Haynes et al. studied 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels. Haynes et al. found that for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold (pg 1863, ¶ 2, Figure 1). Therefore, one skilled in the art cannot predict that the EGFL6 mRNA transcript levels determined in various cancerous tissues are indicative of EGFL6 polypeptide (SEQ ID NO: 24) expression in cancerous cells. Undue experimentation is required by the

skilled artisan to detect EGFL6 polypeptide expression in all possible tumor tissues/cells, other than colon cancer.

Additionally, a large quantity of experimentation would be required of the skilled artisan to detect cancerous cells in any sample other than a cell or tissue. In Example 6 of the specification, the *in situ* hybridization studies are performed directly with normal and cancerous tissues. There are no methods or working examples in the specification to indicate that the EGFL6 polypeptide of SEQ ID NO: 24 is present in blood, serum, lymphatic fluid, urine, or cerebrospinal fluid. Undue experimentation would be required of one skilled in the art to develop and carry out studies examining EGFL6 polypeptide expression in various body fluids other than cells or tissue.

Furthermore, regarding the claim recitation of any fragment of SEQ ID NO: 24 (for example, claim 13, line 2), the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However,

Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Daniel et al. (Virology 202: 540-549, 1994) also disclose that primary amino acid sequences do not predict antigenic determinants and therefore, changing the amino acid sequence of a polypeptide may also affect antigenicity (pg 540, 547).

Additionally, the Examiner has interpreted claim 43 to encompass all possible fragments of SEQ ID NO: 24, including fragments of at least 1 amino acid. One skilled in the art cannot predict that all fragments of EGFL6 are exclusive to SEQ ID NO: 24. Non-specific polypeptide fragments of SEQ ID NO: 24 may overlap with the amino acid sequences of other proteins.

Therefore, the skilled artisan would be not be able to determine if the polypeptide fragment-antibody complex detected in the claimed method truly indicates that cells are expressing the EGFL6 polypeptide of SEQ ID NO: 24. Furthermore, the non-specific fragment-antibody expression pattern may not be unique to only cancer cells.

Applicant is encouraged to submit any pre- or post-filing date references or evidence in the form of a declaration under 37 C.F.R. 1.132 to support the specification.

Due to the large quantity of experimentation necessary to detect EGFL6 protein expression in all possible cancers other than colon cancer, to detect a cancerous cell expressing the polypeptide of SEQ ID NO: 24 in all possible biological samples other than cells and tissue, and to generate and detect the infinite number of fragments of SEQ ID NO: 24, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the unpredictability of correlating mRNA transcript levels to protein expression, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 43-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-18 of copending Application No. 09/981,649 and claims 36-40 of copending Application No. 10/112,881. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the '649 and '881 applications and the instant application recite a method of detecting a cancerous cell expressing the polypeptide of SEQ ID NO: 24 or a fragment thereof in a biological sample, comprising (a) contacting the sample with an antibody or fragment thereof that specifically binds to the polypeptide of SEQ ID NO: 24 or a fragment thereof for a time period sufficient to form a complex; and (b) detecting the complex, so that if a complex is detected it indicates the presence of the cancerous cell. The difference between the claims of the '649 and '881 applications and the instant application is that claim 43 of the instant application recites the additional step of comparing polypeptide expression to a standard indicative of cancer, while claim 13 of the '649 application and claim 36 of the '881 application do not. However, all sets of claims recite the step of detecting a cancerous cell expressing the polypeptide of SEQ ID NO: 24 and detection a polypeptide-antibody complex.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 43-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 43-58 are rejected as being indefinite because use of the phrase "or fragment thereof" for both the polypeptide of SEQ ID NO: 24 and an antibody is confusing.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure (EGFL6):

Ford et al. U.S. Patent 6,392,019

Ford et al. U.S. Patent 6,392,018

Greener M. Mol Med Today. 2000 Apr;6(4):139-40.

Yeung G et al. Genomics. 1999 Dec 1;62(2):304-7

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

BEB
Art Unit 1647
28 August 2003